REMARKS

I. Amendments to the Claims

Claims 10-28 are pending, with claims 10 and 17-23 being independent. Claims 10, 17-23, and 26 have been amended, and claims 27 and 28 have been added, all without prejudice to pursue canceled subject matter, if any, in a continuing application, and without disclaimer of any subject matter.

Independent claims 10 and 17-23 have been amended to recite, "wherein said at least one (particulate) immunogen is not covalently coupled to said B subunits." Support for this amendment can be found, among other places, at the top of page 6 in the specification: "In the vaccine according to the present invention the LTB can be used freely admixed with the particulate antigen - a covalent coupling between the antigen and the adjuvant can be established, however, [it] is not needed to attain adequate adjuvant effect." Further support for this concept can be found in Example 1 on pages 6-8 of the specification. There, Applicants describe the separate fabrication of particulate influenza subunit antigen and LTB (B subunits). Reading this separate fabrication and subsequent combination into a vaccine, the skilled artisan would understand that the influenza subunit antigen is not covalently coupled to the B subunits. Accordingly, no new matter has been introduced by this amendment.

Claims 23 and 26 have been amended to recite at least one "particulate" immunogen. Support for this amendment appears throughout the specification and claims as filed, and on page 4, lines 8-22.

New claims 27 and 28 have been added to recite, "wherein the at least one particulate immunogen comprises micelles, rosettes, or a mixture of micelles and rosettes." Support for these new claims can be found, among other places, in the specification at page 4, lines 19-22.

II. Claim Rejections Under 35 U.S.C. § 112

A. "Particulate Immunogen"

The Examiner rejects claims 10-26 as allegedly being vague and indefinite because it is unclear what is encompassed by the term "particulate immunogen." Office Action at page 2. Moreover, "a 'protein or peptide antigen' is being considered to encompass the scope of the term a 'particulate immunogen' for the purposes of this examination." *Id.* Applicants respectfully disagree with these assertions.

The specification clearly teaches what a particulate immunogen is. "As defined herein, 'particulate' means any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms." Specification at page 4, lines 19-20. "More in particular, the term 'particulate immunogen' comprises aggregates, clusters, micelles, virosomes, rosettes, virus-like immunogen particles, and the like." *Id.*, at lines 20-22.

The specification also teaches what a "particulate immunogen" is not. "For example, adjuvant activity towards freely mixed small soluble antigens, such as ovalbumin or the soluble ectodomain of the envelope glycoprotein of human immunodeficiency virus (gp120), is low and often undetectable." Specification at page

4, lines 8-10. If these small soluble antigens were presented as "large aggregated or particulate immunogens," then it is possible that "very powerful adjuvant activity" will be observed. *Id.* at lines 10-12.

Accordingly, in one embodiment of the claimed invention, "particulate immunogen" can be thought of as an "associated" immunogen. Single, small, soluble antigens, single-molecule proteins and peptide antigens, or even simple fusion proteins, would not fit this description, unless perhaps if they are associated together in some way.

The alleged prior art also informs the skilled artisan about the meaning of "particulate immunogen." *Hirst et al.* (WO 90/06366) discloses a fusion protein comprising LTB and an antigen or epitope of a pathogen. *Hirst et al.* at page 2, lines 8-9. A single fusion protein is not a particulate immunogen. *Hirst et al.* discloses, however, that disclosed "fusion proteins fold correctly and assemble into stable pentameric complexes." *Id.* at page 1, lines 33-34. Such pentameric complexes fit Applicants' definition of particulate immunogen: "As defined herein, 'particulate' means any association of . . . antigens characteristic of the respective microorganisms." Specification at page 4, lines 19-22. To ensure that the claims do not read on *Hirst's* disclosure, Applicants have amended the independent claims so that the claimed particulate immunogen is not bound to the B subunits, thereby excluding *Hirst's* fusion proteins.

The Examiner alleges that "a 'protein or peptide antigen' is being considered to encompass the scope of the term a 'particulate immunogen' for the purposes of this

examination." Office Action at page 2. This assumption is incorrect. Moreover, nothing in Applicants' specification limits the claimed particulate immunogens to proteins or peptide antigens. Instead, Applicants request that their claims be given the broadest reasonable interpretation in accordance with M.P.E.P. § 2111.

The Examiner alleges that the rejection of January 10, 2002, regarding "particulate immunogen" was never addressed. Office Action at page 2. Applicants respectfully point out that the Office Action dated January 10, 2002, mistakenly examined canceled claims 1-9, so the rejection was moot.

B. "Adjuvanting Amount"

The Examiner alleges that "adjuvanting amount" renders claims 10-23 vague and indefinite under 35 U.S.C. § 112, ¶ 2. Office Action at page 3. Applicants respectfully disagree.

"Adjuvanting amount" will be perceived by those of ordinary skill in the art to have a meaning similar to "effective amount," a claim term commonly used to identify the amount of active ingredient present in a claimed pharmaceutical composition. To assess whether "effective amount" is definite, "[t]he proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure." M.P.E.P. § 2173.05(c)(III) (citing *In re Mattison,* 509 F.2d 563, 184 U.S.P.Q. (BNA) 484 (C.C.P.A. 1975)). Also, the disclosure should provide "guidelines as to the intended utilities and how the uses could be effected." M.P.E.P. §

2173.05(c)(III). Thus, the skilled artisan should readily see from the disclosure that the "effective amount" is an amount sufficient for a given utility effected by a given means.

By analogy, Applicants satisfy these tests for "adjuvanting amount." In the present disclosure, Applicants employ 2.0 μg of pLTB or hLTB in Examples 2, 3, and 7. Specification at page 8, line 17; page 9, line 9; and page 11, line 6. Furthermore, Applicants identify the utility of the B subunits and the means for effecting that utility:

> The present invention relates to a vaccine containing the B subunits of heat-labile enterotoxin (LTB) of *Escherichia coli* (*E. coli*) as a mucosal immunoadjuvant. The invention relates in particular to a vaccine of this type to prevent influenza infections in humans. However, the invention is not restricted to application in influenza vaccines.

Specification at page 1 (emphases added). From this, the skilled artisan will see that the B subunits can be used as an immunoadjuvant, for example, in a vaccine designed to prevent influenza infections. Without limiting the scope of the term to this amount, utility, or means, Applicants' disclosure satisfies the test for definiteness.

C. "Characteristic of *E. coli*" and "Characteristic of a Micro-Organism"

Claims 10, 16, and 18-20 have been rejected under 35 U.S.C. § 112, ¶ 2, as allegedly being vague and indefinite for reciting "characteristic of *E. coli*." Office Action at page 3. The Examiner suggests amending the claims to read, "from *E. coli*" instead, stating that this term will encompass "recombinant as well as naturally obtained" material. Applicants disagree.

Applicants respectfully contend that the skilled artisan will understand the phrase "B subunits of heat-labile enterotoxin characteristic of *E. coli*" to mean that the

enterotoxin could be isolated from *E. coli,* or could be made recombinantly from DNA taken from *E. coli* and expressed either in *E. coli* or in another host. This understanding matches that of the Examiner. *See* Office Action at page 3 (acknowledging that the subject matter sought to be patented includes "recombinant as well as naturally obtained" B subunits). Also, the skilled artisan will appreciate that B subunits expressed by the DNA of an organism other than *E. coli* will also work in the present invention, especially if they are identical to the B subunits of enterotoxin expressed by the DNA of *E. coli.* There is no disclosure that otherwise identical B subunits should not be used in the present invention, even though they are not "from" *E. coli.* In fact, the specification reveals the similar structure of enterotoxin and cholera toxin, made by different organisms. *See* specification at page 2, lines 30-32. The proposed language, "from *E. coli,*" therefore, is too narrow to cover the full scope of Applicants' disclosed invention.

Similarly, the Examiner rejects "characteristic of a micro-organism" in claim 14. Office Action at page 3. Again, Applicants contend that a "particulate immunogen [that] is characteristic of a micro-organism" need not be isolated from or expressed by the DNA of that micro-organism. For example, the DNA of a non-pathogenic organism could express an immunogenic epitope that is "characteristic of a micro-organism which causes a disease which is transmitted by mucosal infection" as recited in claim 14. It would be far safer to work with a non-pathogenic organism in the large-scale manufacture of a vaccine, even if recombinant methods are used. To show that such concepts fall within the scope of the claimed invention, the specification mentions "well-defined subunit vaccines" and "synthetic vaccines" on page 1, lines 20-21. Accordingly,

the proposed language "from a micro-organism" is too narrow to cover Applicants' disclosed invention.

D. "Derived"

Claim 13 has been rejected under 35 U.S.C. § 112, ¶ 2 as allegedly being indefinite for reciting "derived." Office Action at page 3. Specifically, "The term 'derived' does not provide the character or properties from the source that are to be retained in the final product." *Id.* Applicants respectfully point out that the claim actually recites "wherein the at least one particulate immunogen is derived from at least one infective agent which causes a disease which is transmitted by mucosal infection." Claim 13. Consequently, the "derived" matter must retain the character and properties of a particulate immunogen. If it does not function as an immunogen, then the "deriving" has gone too far. For example, paper is derived from wood; however, a "building material derived from wood" does not include writing paper. *Compare* Office Action at page 3. The proposed language "isolated from" is too narrow, because the immunogen can be made recombinantly. Such an immunogen need not be "isolated from" the infective agent. *See* specification at page 2, lines 1-4.

E. "Common Mucosal Immune Response"

Claims 18 and 20 have been rejected under 35 U.S.C. § 112, ¶ 2, as allegedly being vague and indefinite for reciting "common mucosal immune response." Office Action at page 4. The Examiner suggests amending these claims to recite "a T-cell

independent IgG and a secretory IgA local response." *Id.* Applicants respectfully traverse the rejection and resist this suggestion.

This claim language is definite. "The test for definiteness under 35 U.S.C. 112, second paragraph is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.' " M.P.E.P. § 2173.02 (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.* 806 F.2d 1565, 1576, 1 U.S.P.Q.2d (BNA) 1081, 1088 (Fed. Cir. 1986)). The specification provides an understanding of the rejected claim language, among other places, at page 5, lines 19-23: "Remarkably, it was found that by i.n. immunisation according to the present invention the so-called common mucosal immune system is activated which results in secretion of S-IgA not only at the site [of] application (i.n.) but also in distant mucosal tissues (e.g. in the vaginal mucosal tissue)." Thus, a skilled artisan could measure whether acts fall inside or outside the scope of the claim term, for example, by looking for secretion of S-IgA at the site of application and in distant mucosal tissues.

The Examiner's suggestion impinges on Applicants' right to act as lexicographer. See M.P.E.P. § 2173.01 ("A fundamental principle contained in 35 U.S.C. § 112, second paragraph is that applicants are their own lexicographers.") Moreover, the Examiner's suggested language could be misconstrued to limit the scope of the claims. The specification reveals that S-IgA is secreted both at the cite of administration and in distant mucosal tissue. *See* specification at page 5, lines 19-23. The Examiner's suggested language could be misconstrued, since it ignores a "local" S-IgA response at a "distant" mucosal site in the body.

For these reasons, Applicants decline to follow the Examiner's suggestion, and ask that the rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 102

A. *Tamura et al.*

Claims 10 and 12-26 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Tamura et al.* (U.S. Patent No. 5,182,109). Office Action at page 4. The Examiner rejects Applicants' argument that *Tamura et al.* does not teach a particulate immunogen. *Id.* at page 5. Also, the Examiner discounts Applicants' argument that *Tamura et al.* fails to disclose B subunits "free of A subunit." *Id.* at page 6.

Tamura et al. does not describe "particulate immunogens." Moreover, the Examiner has the burden to show that *Tamura et al.* describes this limitation, even though the limitation has been rejected as indefinite. "A claim limitation which is considered indefinite cannot be disregarded." M.P.E.P. § 2143.03 (referring to the obviousness analysis under 35 U.S.C. § 103); *see also* M.P.E.P. § 2131 (requiring "each and every element" to be found in the prior art for the claim to be anticipated.). However, to meet this burden, the Examiner merely asserts that "The HA influenza antigens disclosed by Tamura fall under" Applicants' definition of particulate immunogen. Office Action at page 6.

Tamura et al. fails to describe anything other than unassociated, non-particulate immunogens. For influenza vaccine, for example, "a vaccine [can be made] comprising

the whole or a part of hemagglutinin (HA), . . . which [is] obtainable by purifying a virus, which is grown in embryonated eggs, with ether and detergent, or by genetic engineering techniques or chemical synthesis." *Tamura et al.* at col. 9, lines 1-6. Nothing within this disclosure describes aggregation or association of the antigen. In fact, the method of isolating and purifying hemagglutinin antigen employed by *Tamura et al.* yields "soluble HA antigen." *See* specification at page 3, line 20 to page 4, line 2.

Tamura et al. prepares the HA vaccines by treating influenza virus "with ether to remove the lipids." *Tamura et al.* at col. 10, lines 18-19. This method was first described by *Davenport et al., J. Lab. & Clin. Med.* 63(1):5-13 (1964) (submitted with the IDS filed on September 26, 2000). Solidifying the connection of *Tamura's* ether method to the disclosure of *Davenport et al.,* Dr. Tamura's articles of record in this application cite *Davenport et al.* for the preparation of HA. *See, for example, Tamura et al., J. Immunol.,* 149(3):981-88, 982 (1992). After extracting with ether, *Davenport* describes precipitating "soluble antigen." *Davenport et al.* at page 6. *Davenport et al.* prepares a vaccine of isolated HA by centrifuging, and then dialyzing and diluting the supernatant, showing the antigen to be soluble, since it resides in the supernatant. *See Davenport et al.* at page 6. Because *Davenport's* antigen is soluble, *Tamura et al.* simply fails to describe, teach, or suggest particulate immunogens.

Furthermore, *Tamura et al.* does not describe "B subunits [] free of A subunit." *Tamura et al.* uses cholera B subunit ("CTB") from Sigma Chemical Company. "The CTB preparation used in the present experiments did not reveal any detectable contamination with A subunit as determined by SDS-polyacrylamide gel electophoresis

[SDS-PAGE]." *Tamura et al.* at col. 10, lines 25-28 (emphasis added). However, the most-recent Sigma catalogue reveals that Sigma's B subunit is only "≥95%" pure by SDS-PAGE. SIGMA CHEMICAL COMPANY CATALOGUE 505-06, 2002-2003. Thus, Sigma's CTB could contain as much as 5% of A subunit, because this amount falls below the sensitivity of SDS-PAGE. Significantly, Dr. Tamura himself concluded that his prior studies were tainted by the presence of 0.1% CT in Sigma's CTB. *See Tamura et al., Vaccine* 12(5):419-26, 424 (1994). Taking the prior art as a whole, the skilled artisan would not conclude that *Tamura et al.* describes "B subunits [] free of A subunit."

At least because *Tamura et al.* does not describe particulate immunogens or B subunit free of toxic A subunit, this rejection should be withdrawn.

B. *Hirst et al.*

Claims 10-24 and 24 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Hirst et al.* (WO 90/06366). Office Action at page 7. The Examiner maintains that the fusion proteins taught by *Hirst et al.* fall within Applicants' definition of particulate immunogen. Office Action at page 8. Also, the Examiner alleges that *Hirst's* B subunit would be free of holotoxin. *Id.* Applicants respectfully disagree with this rejection.

Hirst et al. discloses a fusion protein comprising LTB and an antigen or epitope of a pathogen. *Hirst et al.* at page 2, lines 8-9. A single fusion protein is not a particulate immunogen. *Hirst et al.* discloses, however, that disclosed "fusion proteins fold correctly and assemble into stable pentameric complexes." *Id.* at page 1, lines 33-34.

To ensure that the claimed particulate immunogens do not read on *Hirst's* disclosure, Applicants have amended their independent claims to state that the at least one particulate immunogen is not bound to the B subunits. This language excludes the fusion proteins disclosed by *Hirst et al.*

Accordingly, the rejection over *Hirst et al.* should be withdrawn.

C. *Kikuta et al.* or *Hirabayashi et al.*

Claims 10 and 12-26 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Kikuta et al.* (*Vaccine,* 8:595-599 (1990)) or *Hirabayashi et al.* (*Vaccine,* 8:243-248 (1990)). Office Action at page 8. The Examiner relies on disclosure in both documents stating that the purchased B subunit of cholera toxin were devoid of any detectable contamination with A subunit. *Id.* Applicants respectfully traverse this rejection.

Neither *Kikuta et al.* nor *Hirabayashi et al.* disclose, teach, or suggest particulate immunogens. Both authors employ the method of *Davenport et al., J. Lab. Clin. Med.,* 63(1):5-13 (1964), to isolate influenza immunogen. *See Kikuta et al.* at page 595; *and Hirabayashi et al.* at page 243. This method provides "soluble HA antigen" (specification at page 3, lines 23-28), not the "particulate immunogen" of Applicants' claimed invention.

Because neither *Kikuta et al.* nor *Hirabayashi et al.* describe particulate immunogens, rejections over these documents should be withdrawn.

D. *Fujisawa et al.*

Claims 10-23 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Fujisawa et al.* (U.S. Patent No. 5,241,053). Office Action at page 9. The Examiner rejects the arguments that this document does not describe particulate immunogens or compositions free of holotoxin. *Id.* at pages 10-11. Applicants respectfully disagree.

In addition to failing to describe particulate immunogens and compositions free of holotoxin, *Fujisawa et al.* also fails to describe compositions in which the "at least one particulate immunogen is not bound to said B subunits," as claimed in pending claim 10. *Fujisawa* teaches, instead, fusion proteins of "heat-labile enterotoxin B subunit (LTB) and a protein" which acts as an antigen. *Fujisawa et al.* at col. 2, lines 14-19. Thus, *Fujisawa's* antigen is bound directly to the B subunit to form the fusion protein. Even if *Fujisawa et al.* were to teach a particulate immunogen, *Fujisawa et al.* cannot describe such an immunogen that is not bound to B subunits.

Accordingly, the rejection over *Fujisawa et al.* should be withdrawn.

CONCLUSION

Applicants file this Amendment with a Request for Continued Examination under 37 C.F.R. § 1.114. Applicants respectfully request reconsideration of this application in view of the amendments and remarks set forth above and the timely allowance of all pending claims.

A Petition for Extension of Time (Three Months) accompanies this Amendment. Please grant any extensions of time required to enter this Amendment and charge any additional fees required under 37 C.F.R. §§ 1.16 or 1.17 to our Deposit Account No. 06-0916.

Respectfully submitted,

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